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Postpartum Thyroiditis In Palestinian Women

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Committee Decision

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This thesis was defended successfully on June, 19, 2002. and approved by:

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Dedication

To My Dear Wife, Sons; Bara,

Abdul-Rahim & My Daughter, Ragad,

For

There

Encouragement And Patience, With Love

And

Respect

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Abstract:

To the best of my knowledge there is no screening for postpartum thyroiditis (PPT) in Palestine up to date .The aim of this study was to establish a base line data regarding PPT incidence , and to determine possible risk factors.

This study shows that the screening program system faced many problems regarding sampling as well as handling of specimens, and also in follow up and communication with people. From May 2000 to May 2001, there was 101 pregnant women screened for PPT by measuring the TSH hormone by immuno-radiometric assay (IRMA) method. Four cases were diagnosed as suspected PPT as TSH concentration was undetectable, incidence about 4%. This incidence is in the same range of reported incidence in most countries. About 17.8% of screened cases were classified in the range less

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than 0.5 mIu/ml for TSH level in postpartum period.

Although our screening program for PPT has benefited pregnant women to some extent, it seems that this subject need more wide screening with more cases, tests, and budgets. To achieve this goal, cooperation between all primary health care providers, to pregnant women in prenatal and PP period, is definitely needed.

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List of abbreviations

(Ab):	Antibody.
(AITD):	Autoimmune Thyroid Disorders.
(cAMP):	Cyclic Adenine Mono Phosphate.
(CD4+):	Cluster of Differentiation, (marker of T helper cells).
(CD8+):	Cluster of Differentiation, (marker of cytotoxic T lymphocyt).
(cDNA):	Complementary Deoxyribo Nucleic Acid.
(CPM):	Count Per Minute.
(FSH):	Follicle-Stimulating Hormone.
(HCG):	Human Chorionic Gonadotropin.
(HLA):	Human Leukocyte Antigen.
(HPLC):	High-Performance Liquid Chromatography.
(I):	Iodine.
(Ig):	Immunoglobulin.
(IRMA):	Immunoradiometric assay.
(LH):	Luteinizing Hormone.
(MHC):	Major Histocompatibility Class.
(NK):	Natural Killer cells.
(Pb):	Lead metal.
(PCR):	Polymerase Chain Reaction.
(PPT):	Postpartum Thyroiditis.
(PPTD):	Postpartum Thyroid Disease.
(RIA):	Radioimmunoassay.
(T3):	Triiodothyronine.
(T4):	Thyroxine.
(TBG):	Thyroxine Binding Globulin.
(Tg):	Thyroglobulin.
(TPO):	Thyroid Peroxidase.
(TRH):	Thyrotropin-Releasing Hormone.
(TSH):	Thyroid Stimulating Hormone.

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Chapter One
Literature Review and Aim of Study

1.1 Introduction:

The most common cause of thyroid disorders worldwide (in areas not deficient in iodine) is autoimmune processes, ranging from hyperthyroidism (excessive amount of thyroid gland hormone) to hypothyroidism (insufficient amount of thyroid gland hormone).

The spontaneous development of antibodies to antigenic components of the thyroid gland is a well - established feature of autoimmune (the immune system attacks the body's own tissues) thyroid disease. (Braverman *etal.*, 1991).

Patients with autoimmune thyroiditis have abnormalities in thyroid function of widely varying severity and frequency (Livolsi & Loger, 1981).

Autoimmune thyroiditis includes atrophic autoimmune thyroiditis, goitrous autoimmune thyroiditis, and postpartum as well as silent (painless) thyroiditis (Braverman *etal.*, 1991).

1.2 Antibodies in autoimmune thyroid disease

The cloning and sequencing of the genes that encode the three major thyroid antigens -thyroglobulin, thyroid peroxidase and the thyroid stimulating hormone receptor (TSH recepter) have made possible detailed characterization of autoantibodies antithyroglobulin antibody and antithyroid peroxidase or antimicrosomal antibody (Fauci *etal*,1998).

Antibodies to thyroid peroxidase are capable of inhibiting the activity of the enzyme and therefore are a potential cause of thyroid dysfunction (Kohno *etal*, 1986).

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1.3 Antibodies to the thyroid microsomal antigen

The microsomal antigen is a component of the exocytotic vesicles in which newly synthesized thyroglobulin is transfered to the follicular lumen (Roitt *etal*, 1964). In this process, the antigenic material fuses with the thyroid follicular cell membrane, thus explaining the restriction of the antigen, to the apical (lumen) portion of the membrane (khoury *etal*, 1984). The microsomal antigen is now known to be thyroid peroxidase (TPO), and it is by this pathway that the apical cell surface acquires peroxidase (Ekholm, 1990).

Typically in women who have postpartum thyroiditis, anti-TPO antibodies titers decline during pregnancy and increase postpartum. Clinically, these women develop hypothyroidism 2-4 months after delivery; in some cases, it is preceded by an evanescent episode of thyrotoxicosis .The serum antibodies, especially anti-TPO, are an indicator of the possibility of postpartum development of autoimmune thyroid disease (Amino *etal.*, 1982, 1985).

1.4 Thyroid Peroxidase

Thyroid peroxidase (TPO) is a membrane - bound, glycosylated, hemoprotein enzyme that plays a key role in thyroid hormone biosynthesis by catalyzing both the iodination of tyrosyl residues and the coupling of iodotyrosyl residues in thyroglobulin to form T4 and T3. Until 1985 this was considered to be its only the role in the thyroid; it was then reported, however, that TPO is closely related to, if not identical with the thyroid microsomal antigen associated with the antithyroid microsomal autoantibodies found in the serum of many patients with autoimmune thyroid disease(Czarnocka *etal.*,1985 & Kotani *etal.*,1986).

The thyroid peroxidase gene was mapped to the short arm of chromosome 2. Two forms of human TPO cDNAs were found; the

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longest cDNA encoded a protein of 933 amino acids, referred to as human TPO-1, and the shorter cDNA encoded a similar protein lacking 57 amino acid in the middle of the sequence, referred to as TPO-2(Braverman *etal*,1991).

Antibodies to thyroid peroxidase are capable of inhibiting the activity of the enzyme and therefore are a potential cause of thyroid dysfunction.These are complement-fixing antibodies that induce cytotoxic changes in cultured thyroid cells and probably in vivo (Kohno *etal*.,1986).

1.5 Factors affecting maternal thyroid function in normal pregnancy

In normal pregnancy, several physiological changes can have an impact on the maternal thyroid function and thyroid hormone metabolism and may represent physiological adaptation to optimise maternal thyroid status for fetal development. A proper understanding of the nature and magnitude of these changes is essential for an appropriate interpretation of thyroid function tests in pregnancy.

1-Effect of human chorionic gonadotropin on thyroid function:

Human chorionic gonadotropin (HCG) is comprised of two subunits, termed alpha and beta chains. The alpha subunit is shared with three other glycoprotein hormones, namely TSH, LH, and FSH. There is structural similarity between the beta subunit of HCG and of TSH and in vitro bioassays indicate that HCG has intrinsic thyroid stimulating activity (Hershman, 1992; Kimura *etal*, 1990).

Concerning normal pregnancy, the thyrotropic role of HCG is illustrated in figure1.1.The figure shows the inverse relationship between serum HCG level and the TSH. In 18% of otherwise euthyroid pregnant women at this time of gestation, serum TSH may even be

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transiently lowered below the normal range (Glinoer *etal.*, 1993; Glinoer, 1995).

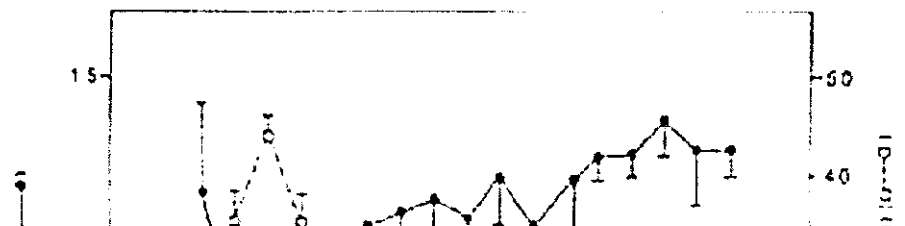

Figure 1.1: Serum TSH and HCG as a function of gestational age. Between 8 and 14 weeks gestation the changes in HCG and TSH levels are mirror images of each other, and there is a significant negative correlation between the individual TSH and HCG levels. From (Glinoer *etal.*,1990).

2- Changes in circulation thyroid hormone binding protein:

Thyroxine-binding globulin (TBG), a glycoprotein synthesised in the liver, binds approximately 70% of circulating T4 and T3. The remainder of circulating thyroid hormone is bound to thyroid-binding pre-albumin (transthyretin) and albumin. Due to the large fraction of circulating thyroid hormone that is bound to serum proteins, changes in the serum concentration of these proteins significantly influence total hormone measurements (Brent, 1997; Braverman *etal.*, 1991).

The increase in total serum T4 and T3 which occurs during pregnancy is due to an increase of TBG in the serum, this change begins to appear early, and TBG concentrations are doubled by 16-20 weaks of gestation (Glinoer, 1997).

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3-Changes in thyroid hormone profile during pregnancy

Table 1.1 shows the effect of pregnancy on thyroid hormone total and free T4 and T3, also TSH and thyroglobulin (Braverman *et al.*, 1991).

Table 1.1: Effect of Pregnancy on Thyroid-Function Tests.

Test	Effect
Serum total T4concentration	Increased
Thyroid hormone-binding ratio (T3-resin uptake)	Decreased
Serum free T4 concentration	No change*
Serum total T3 concentration	Increased
Serum TSH concentration	No change*
Serum thyroglobulin concentration	Increased

*Serum free T4 concentration tend to decline and serum TSH concentration tend to increase slightly during gestation, but most values are within the reference range for nonpregnant subjects. From (Braverman *etal.*, 1991).

4- Pregnancy -induced immune suppression

The alterations in maternal immune system which permit the successful implantation of the fetal allograft have not been definitively identified. However,the factors leading to this immune tolerance seen likely to be partially responsible for the generalized improvement in autoimmune thyroid disease which is so characteristic of the pregnant state. Table 1.2 summarized the main effects of pregnancy on lymphocyte subsets in patients with and without thyroid autoantibodies (Stagnaro-Green *etal.*, 1992, Bech *etal.*, 1991, Simeone *etal.*, 1990, DeGroot & Quintans, 1989; Sridama *etal.*, 1982).

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Table1.2: Effects of pregnancy on lymphocyte subsets in patients with thyroid autoantibodies.

1. Decrease CD4+ and increased CD8+T cells in all patients.
2. Increase in CD29+/CD45RA+ ratio (supressor-inducer Tcell function) postpartum in all patients.
3. Decrease in TPO-and Tg Ab during pregnancy and a marked increase postpartum.
4. In patients who develop postpartum thyroid disease: Thyroid antibodies are higher during and after pregnancy. There is an increased prevalence of HLADR3+ antigens.

Table 1.3 summarizes the various types of autoimmune thyroid disease which can be expected in the pregnant and postpartum population.

Table 1.3 Autoimmune Thyroid Disease During Pregnancy and Postpartum Period

Primary hypothyroidism: a- Thyroid destruction (Hashimoto's disease) b- Circulating TSH- receptor –blocking antibody.
Asymptomatic (euthyroid) autoimmune disease: a-Increased risk of developing subclinical hypothyroidism during pregnancy. b- Increased risk of spontaneous abortion.
Postpartum thyroid disease (PPTD): a- Hyperthyroidism. b- Hypothyroidism. c- Combinations.
Grave's Disease: a-Pre-existing. b- Gestational exacerbation and remission. c- Postpartum exacerbation.

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1.6 Postpartum Thyroid Disease

Postpartum thyroiditis is an autoimmune disorder characterized by a destructive lymphocytic infiltration of the thyroid gland, very often with accompanying circulating thyroid autoantibodies, which can manifest itself as transient hyperthyroidism, transient hypothyroidism, or permanent hypothyroidism. These manifestations result from activation of immunological changes that occur in the first postpartum year (Amino *etal*., 1999).

According to Lazarus, postpartum thyroid dysfunction is characterized by transient hyperthyroidism occuring about 14 weeks postpartum, followed by transient hypothyroidism that present at 19 weeks. Hyper–or hypothyroidism may occur alone. The condition,a destructive thyroiditis, predominantly occur in patients with positive thyroid peroxidase (TPO) auto-antibody (the microsomal antibody) seen in 10 %of women at approximately 16 weeks of gestation (Lazarus, 1998).

The titer of these antibodies is known to decrease during gestation, but increases dramatically in the postpartum period. However , only about 50 % of women found to be TPO antibody positive during pregnancy will develop postpartum thyroid disease (PPTD) .Some cases of PPTD have occurred in the absence of TPO antibodies , suggesting a non –immune cause , which is , as yet ,unknown (Lazarus ,1998) .

Therefore, postpartum thyroiditis has three phases:

1 - Hypothyroidism.

2 - Hyperthyroidism.

3 - Recovery.

In some patients the thyrotoxic or hypothyroid phase either does not occur, or is not recognized. Although recovery is usual, recurrent episodes of hypothyroidism and permanent hypothyroidism

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are found in about 25 %of patients observed for as long as four years (Luboshitzky *etal.*, 1998).

1.6.1 Incidence and prevalence:

The postpartum thyroid dysfunction has been described in many countries and has been reviewed. Most reports have described relatively small number of patients who were followed over short periods of time .This has created a problem in defining the incidence of the condition , although it is now accepted that it occurs in 5 –9 % of unselected women during the first year of postpartum (Lazarus, 1998;Sakaihara *et al.*, 2000).

Table1. 4 illustrates that the reported prevalence of PPT varies from 1.1 % to 16.7 %. The marked diversity in prevalence may to some extent, reflect geographic differences. However, much of this variation reflects differences in duration of follow-up. Thus, terminating a prevalence study at 3 months postpartum will probably miss the majority of cases of PPT, and, therefore, underestimate its true prevalence. It can be assumed that the more frequent the sampling and the longer the duration of follow-up postpartum, the greater the prevalence of diagnosed postpartum thyroiditis (Stagnaro-Green, 1993).

1.6.2. Epidemiology of PPT

Any review of the epidemiology of thyroid disorders is complicated by problems of definition, selection criteria, the influence of age, sex, and environmental factors, and different techniques used for the measurement of thyroid function.

Considerable variation exists in the reported frequency and distribution of thyroid antibodies, the reasons for these variations include differences in techniques of detection, definition of significant

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titers, and inherent differences in the populations selected for screening.

Table1. 4: Prevalence of PPT

Study	Year	Country	Length of follow up (month)	No of Patiants	Screen in Pregnancy +	PPT(%)
Amino *etal*	1982	Japan	6	507	N	5.5
Jansson *etal*	1984	Sweden	5	460	N	6.5
Freeman *etal*	1986	USA	3	212	N	1.9
Nikolai *etal*	1987	USA	3	238	N	6.7
Lervang *etal*	1987	Denmark	12	591/69*	N	3.9
Fung *etal*	1988	UK	12	901/220*	Y	16.7
Rasmussen *etal*	1990	Denmark	12	736/56*	Y	3.3
Rajatanavin *etal*	1990	Thailand	12	812/70*	N	1.1
Roti *etal*	1991	Italy	12	372	N	4.8
Walfish *etal*	1992	Canada	12	1376	N	6.0
Stagnaro-Green *etal*	1992	USA	6	545/70*	Y	8.8

□*Total number of patients screened /total number of patients followed prospectively

□+Refer to whether or not patients were first seen while pregnant (Y= yes, N= no).

□ (From Stagnaro –Green A, 1993).

PPT usually is manifest as a temporary episode of hypothyroidism that develops 4 – 8 month postpartum, which may be preceded by a short episode of hyperthyroidism. During the hyperthyroid phase, up take of radioactive iodine is reduced. The presence of antimicrosomal antibodies in pregnancy increases the risk of developing postpartum thyroiditis, and lymphocytic infiltration of the thyroid has been observed. PPT is, therefore, another manifestation of autoimmune thyroid disease (Braverman *etal.*, 1991).

Several studies in unselected pregnant women indicate a prevalence of PPT of (4 –7) %, although in South Wales the prevalence is as high as 16.7% (Jansson *etal.*, 1988). In prospective studies, 20% to 30% of affected women develop permanent thyroid impairment in the following years (Othman *etal.*, 1990).

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1.6.3. Etiology of PPT

Several studies show the relationship between PPT and the following:

1- Thyroid autoantibodies.

2- Human leukocyte antigen (HLA) serotypes.

3- T–cell phenotypic changes in women who develop PPT.

4- Natural killer (NK) cells.

5- Immunoglobulin (Ig) sub classes and affinity.

6-Thyroid iodine content.

7-Type 1 diabetes mellitus.

The association of PPT with HLA alleles (HLA-DR3, 4, 5) was suggested to be important in identifying women positive for antithyroid microsomal antibodies who later developed PPT (Farid &Balazs, 1988). This was not confirmed in other studies, which instead showed the importance of these antibodies 2 –4 months after delivery in identifying those women at high risk for PPT (Vargas *etal.*, 1988).

HLA haplotype studies show an increase in the frequancy of HLA –DR3, 5 in PPT (Farid *etal*, 1983).

More recently, Kologlu etal described an association of a combination of HLA–A1, B8, DR3, and HLA-B8, DR3 in women who had PPT (Premawardhana *etal.*, 2000).

Sridama *etal* found a decrease in helper T lymphocytes (CD4+) during pregnancy. They postulated that the alteration of the CD4+. T cells may be important in the altered immune status of pregnancy (Sridama *etal.*, 1982).

Briones-Urbina *etal* found an increase in IgG1, 2, 4 in women who developed PPT.They also found an increase in antimicrosomal antibody –related IgG1, 4. They concluded that the polyclonality of the antibody response supports the notion of the antibodies as useful

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markers, but not etiologic agents of the disease (Briones-Urbinal *etal.*, 1990).

In a prospective analysis, Hidaka *etal* found that women who developed PPT had a significant increase in NK activity as compared to women who were one month postpartum. At this point the role of NK cells in the etiology of PPT remains tenuous (Hidaka *etal.*, 1992).

In 1990, Kampe *etal* evaluated the effect of iodide administration on the developed of PPT in women who were thyroid antibodies positive. They found that the administration of iodide did not alter the incidence of the disorder but that iodide-treated women who developed PPT had more marked thyroid hormonal abnormalities. They concluded that iodide does not play an important role in the pathogenesis of PPT (Kampe *etal.*, 1990).

Women with type 1 diabetes mellitus are at particularly high risk for developing PPT. Bech *etal* investigated the prevalence of PPT in Danish women with type 1 diabetes mellitus. They found a 10.5% prevalence of PPT in women with pre-existing type1 diabetes. This reflected a three – fold increase in the prevalence of PPT as compared to an earlier investigation of PPT in healthy Danish women (Stagnaro-Green, 1993).

1.7 Postpartum thyroiditis and genetics

Genes are chosen to test for linkage studies with a disorder because they may influence one or more of the continuous variables or empirically in all–or none traits, such as autoimmune thyroid disease (Braverman *etal.*, 1991).

Most autoimmune disorders, including those of thyroid are associated with major histocompatibility complex (MHC) class II alleles. Only subacute thyroiditis has been firmly related to a class I alleles.

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The DNA sequences of almost all HLA –DR, DQ, and DP alleles (figure1.2) were determined after amplification of their polymorphic domains by polymerase chain reaction PCR (White *etal.*, 1989, &Farid *etal.*, 1990).

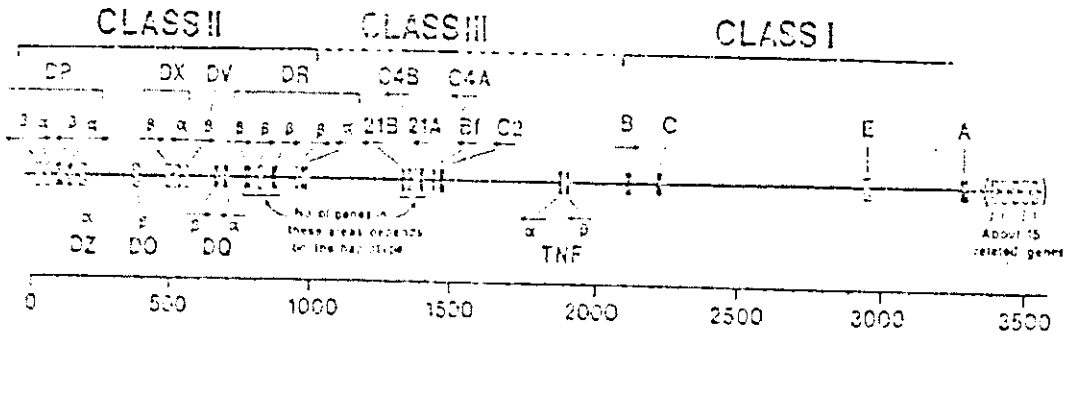

Figure 1.2: Physical map of the human major histocompatibility class (MHC) genes: class I, II, and III on chromosome 6.Class II contains the DR, DQ, andDP sets.From (Braverman *etal.*, 1991).

The sequences of class II molecules from patients with autoimmune disorders did not contain any mutants compared with wildetype .What has emerged,however,is that variations in certain residues may have important implications on autoimmunity(Todd *etal.*, 1987&Farid *etal* .,1990).

The association of HLA alleles with postpartum thyroiditis closely reflects what was outlined previously for Hashimoto's disease (Farid *etal.*, 1988). Thus, postpartum thyroiditis has been related to HLA-DR3 in the Welsh, -DR4 in Sweden and Canadian Newfound landers,and –DR5 in Canadians form Tronto (Farid *etal.*,1988 &Vargas *etal.*,1988) .

It is nevertheless unclear why in people with the same HLA genetic susceptibility, one disease is transient and the other is chronic? It is also unclear why in North America, a transient thyrotoxic phase is the presenting feature of the disease, where as this is much less common in Europe and Japan? (Farid *etal.*, 1988). Variations in dietary iodide may be important.HLA-DR4 was suggested to be

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important in identifying women positive for antithyroid microsomal antibodies who later developed postpartum thyroiditis in a Swedish study (Farid *etal.*, 1988).This was not confirmed in other studies, which instead showed the importance of these antibodies 2 to 4 months after delivery in identifying those women at high risk for postpartum thyroiditis (Vargas *etal.*,1988).Silent thyroiditis unrelated to pregnancy appears to be a milder form of postpartum thyroiditis and maintains similar HLA associations.

1.8 Postpartum thyroiditis and silent thyroiditis relationship

Silent thyroiditis is a term used to describe lymphocytic thyroiditis with transient throtoxicosis. Silent thyroiditis and PPT with transient thyrotoxicosis are similar in many aspects, although PPT has a much wider clinical spectrum in that it includes transient thyrotoxicosis, transient hypothyroidism, persistent hypothyroidism, and euthyroid goiter (Braverman *etal.*, 1991).

A significant percentage of patients who have silent thyroiditis have personal or family histories of autoimmune thyroid disease. HLA haplotype studies show an increase in the frequency of HLA-DR3 in silent thyroiditis and HLA-DR3 and DR5 in PPT (Farid *etal.*, 1983).

In silent thyroiditis the titers of thyroid antibodies are low or none detectable, there may be a seasonal geographic variation in incidence and recovery is usually complete. The situation is different in regards to postpartum thyroiditis, changes in the titers of antithyroid antibodies and thyroid-stimulating antibodies are common during pregnancy and after delivery in women with autoimmune thyroiditis (Braverman *etal.*, 1991). So the most important clinical differences between silent and postpartum thyroiditis are that postpartum thyroiditis is associated with a higher frequency of positive tests for antithyroid antibodies.

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When thyrotoxicosis is present, silent, postpartum and subacute thyroiditis all have similar clinical courses. Silent thyroiditis and PPT are indistinguishable forms of lymphocytic thyroiditis, where as subacute thyroiditis is charachterized by granulomatous gaint cell infiltration (Braverman *etal.*, 1991).

1.9 Postpartum pitutary necrosis and lymphocytic hypophysitis

Thyroid dysfunction occurs more frequently in the peripartum or postpartum period than during pregnancy. One of the earliest causes of postpartum thyroid dysfunction to be recognized was postpartum pituitary necrosis. This syndrome is caused by excessive vaginal bleeding and hypotension at the time of delivery. Hypothyroidism may develop insidiously, and often is preceded by symptoms of prolactin and gonadotropin deficiency.

Another cause of postpartum thyroid dysfunction is lymphocytic hypophysitis. Although rare, it may be more common than pituitary necrosis in regions where adequate obstetric care is available. Lymphocytic hypophysitis often occurs in the latter part of gestation or several months after delivery. It is characterized by enlargement of the sella turcica, headache, and the development of hypopituitarism. There may be signs of increased intracranial pressure or optic compression (Braverman *etal.*, 1991).

1.10 Clinical features of postpartum grave's disease and postpartum thyroiditis

Grave's disease is a disease with hyperthyroidism associated with a diffusely hyperplastic goiter resulting from production of an antibody directed against the thyroid –stimulating hormone receptor, which acts as an agonist of TSH (Volpe,1990 &Fauci etal.,1998).

The two forms of postpartum thyroid dysfunction related to thyroid autoimmunity are postpartum Grave's disease and postpartum thyroiditis.

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Postpartum Grave's disease is, by definition, a relapse of typical Grave's disease during the first year after delivery. In these patients, thyrotoxicosis caused by accelerated thyroid hormonogenesis rather than destruction– induced release of thyroid hormone.

Postpartum thyroiditis, in contrast is probably a form of chronic autoimmune thyroiditis. One of the first reports of this syndrome described the development of thyroid enlargement in patients with struma lymphomatosa (goitrous autoimmune thyroiditis) several months after delivery. Many years later, the association of postpartum goiter or enlargement of a preexisting goiter, transient lymphothyroidism, and high titers of antithyroid antibodies was described. Shortly there after, similar patients who had transient thyrotoxicosis before developing hypothyroidism were reported (Braverman etal., 1991).

1.11 Symptoms of PPT

The symptoms associated with PPT are often subtle and difficult to distinguish from symptoms frequently present during the postpartum period. Those women at high risk for PPT are easy to identify because PPT is an autoimmune disease in which most patients have elevated serum levels of thyroid autoantibodies. (Amino *etal.*,1991).

The duration of hypothyroid phase is variable, and symptoms during the hyperthyroid and hypothyroid phases of the illness are often mild in degree and brief in duration. Symptoms of thyroid dysfunction occuring after pregnancy (hypothyroid phase) are, fatigue associated with depression, weight gain, lethargy, poor memory, dry skin, cold intolerance and constipation.

Symptoms during hyperthyroid phase include tachycardia, excessive sweating, rapid post–pregnancy weight loss, tremulousness

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and nervousness (Lazarus *etal.*, 1996; Othman *etal.*, 1990; Gerstein, 1990 & Roti *etal.*, 1992).

Finally, the symptoms of hyperthyroidism and hypothyroidism blend with and are notoriously difficult to separate from other symptoms associated with the postpartum state. Some of the symptoms of hyperthyroidism and hypothyroidism may be found more frequently in postpartum women with PPT and \ or positive TPO–antibodies titers, compared to those without PPT. However, the clinical distinction between these two groups of postpartum women can be quite difficult (Amino *etal.*, 1999).

1.12 Screening for PPT

In general, screening may be defined as testing for the presence of a disease or the risk of a disease when no known signs or symptoms of the disease are present, with the purpose of improving health outcomes in the target population (Eddy, 1991).

Although PPT is common, symptoms during the hyper & hypothyroidism phases of the illness are often mild in degree and brief in duration and, consequently, may not require treatment. When symptoms are moderate or severe in degree they should be recognized clinically, although this will require more education of primary care physicians and postpartum patients about PPT. Which thyroid autoantibody assay should be used for screening and when the assay should be performed have not been completely resolved. Furthermore, there is a lack of knowledge about how to follow patients with a positive antibody assay. Should a serum TSH level be done only when they are symptomatic, or should serial TSH levels be done and, if so, at what intervals?

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Also, and most importantly, there has been no prospective diagnostic and therapeutic trial to date that tells us whether or not a

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screening program would be beneficial. Figure1.3 shows a systematic screening of autoimmune thyroid disease.

Thyroid peroxidase (TPO) antibody is the potential screening test of choice for PPT. Screening for (TPO) would need to occur early in pregnancy in order to identify women who were going to develop PPT before its manifestation. Given the dramatic and well documented decrease in thyroid antibodies during pregnancy, screening at delivery would miss a large percentage of the cases and consequently would have high false negative rate (Amino *etal.*, 1999).

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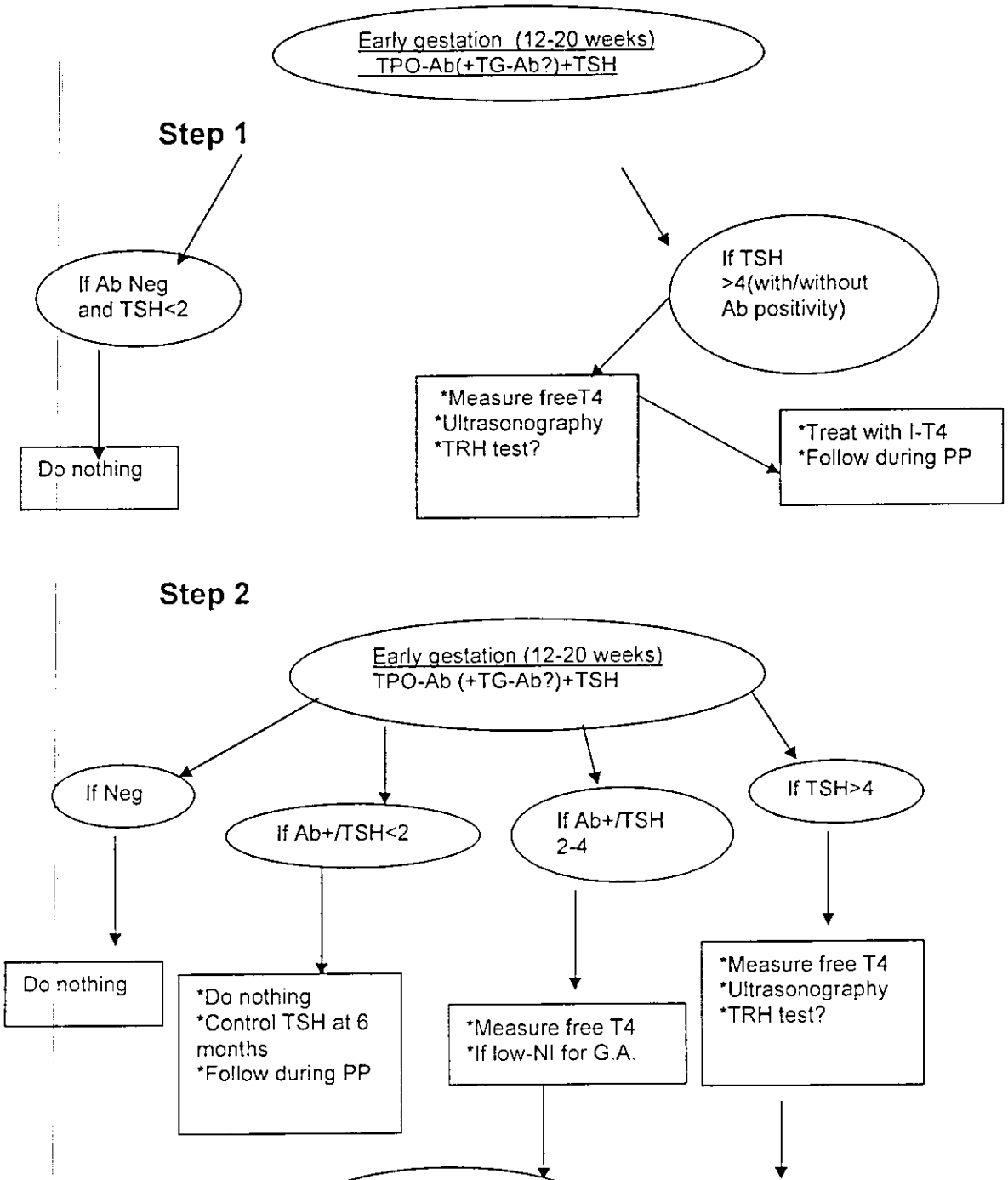

Figure1.3: A proposed two-step algorithm for the systematic screening of autoimmune thyroid disorders (AITD) and hypothyroidism during pregnancy , based on the determination of antithyroperoxidase antibodies (TPO-Ab), antithyroglobulin antibodies (TG-Ab),and serum thyroid stimulating hormone (TSH) concentrations in the first half of gestation.From (Glinoer ,1998).

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1.13 Thyrotropin

Thyroid-stimulating hormone (TSH, thyrotropin) is a 32 kDa glycoprotein secreted by the thyrotrope cells of the anterior pituitary gland (Magner, 1990). The structure of human TSH is similar to that of the pituitary and placental gonadotropins, consisting of an 89-amino acid alpha subunit, which is similar or identical between these hormones, and a 115-amino acid beta subunit, which apparently confers hormonal specificity. The production of the 2 subunits is separately regulated with apparent excess production of the alpha subunit. The TSH molecule has a linear structure consisting of the protein core with carbohydrate side chains; the latter accounts for 16% of the molecular weight.

TSH stimulates production of thyroid hormones by binding to specific thyrocyte membrane receptors, leading to stimulation of cAMP dependent iodine transport and resultant thyroid hormone synthesis (Vassart & Dumont,1992). TSH secretion is stimulated by thyrotropin-releasing hormone (TRH) which is secreted by the hypothalamus and is regulated at both the pituitary and hypothalamic levels by thyroid hormone. Low levels of thyroid hormone lead to increased TSH secretion and elevated thyroid hormone levels lead to decreased TSH secretion.

1.14 Thyroid Function: Normal references hormonal concentrations

During pregnancy, changes in serum thyroid hormones are well documented. Many studies for postpartum thyroiditis have the references for hormone concentration as below:

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Lazarus *etal*, referred to normal ranges for thyroid function as:

F T4: 8 -19 pmol / L

FT3:4.2 - 7.7 pmol /L

TSH: 0.5 - 3.6 mlu /ml

And thyroid dysfunction was defined as follows:

Hyperthyroidism: either suppressed TSH together with FT4 >19 pmol/ L or FT 3 > 7.7 pol / L, or elevated FT3 and FT4 with either set of criteria occurring on one or more occasion.

Hypothyroidism: either TSH > 3.6 mlu /ml together with FT4 < 8 pmol/ L or FT 3 < 4.2 pmol / L or TSH > 10 mlu/ml on one or more occasion (Lazarus *etal.*, 1996).

Another study;by Sakaihara *etal* depends on the normal ranges through out pregnancy and postpartum as below :

FT4: 9 – 25.8 pmol / L at more than 17 gestational weeks.

TSH: 0.2 -6.0 mlu/ml (Sakaihara *etal.*, 2000).

Premawardhana *etal* in their study have the normal value as follows:

FT4:9.8- 23 pmol / L

FT3: 4- 6.8 pmol / L

TSH : 0.5 -5.2 mlu/ml (Premawardhana *etal.*, 2000).

In Caixas *etal* study the TSH reference range was 0.25 -5.0mlu/ml (Caixas *etal.*, 1999).

1.15 Diagnosis of PPT

There are many changes that can occur in thyroid function after pregnancy. It is worthwhile to warn pregnant women with a history of thyroid disease that their underlying disorder may worsen after delivery. Postpartum women with nervousness, depression, lethargy, or emotional lability should have thyroid function tests. The serum TSH concentration should be measured: if abnormal, serum free T4 concentration should be estimated, preferably in the same sample

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used for the TSH measurement. Hypothyroidism is defined as either TSH > 3.6 mlu/ml together with FT4< 8 pmol/L or TSH is 10.0 mlu/ml on one or more occasion (Lazarus etal., 1996).

If thyroid–function tests are compatible with thyrotoxicosis and the patient is not nursing, radioactive iodine uptake should be measured. A low uptake support the diagnosis of postpartum thyroiditis, where as a normal or high value indicates the presence of Grave's disease. Patient with PPT or postpartum Grave's disease should be closely followed up, since their thyroid status usually is unstable. Moreover, unusual variants have been described, for example the sequence of postpartum hypothyroidism followed by thyrotoxicosis.

In summary, PPT diagnosis as:

1- Thyrotoxicosis and hypothyroidism 6 weeks to 6 months postpartum.

2- Usually positive TPO Ab.

3 - Low I^{123} thyroid uptake.

4- Hypoechogenicity on thyroid ultrasound. (Fung *etal.*, 1988&Lazarus,1996).

1.16 Treatment of PPT

Although PPT is common, symptoms during the hyperthyroid and hypothyroid phases of the illness are often mild in degree and brief in duration and consequently, may not require treatment .When symptoms are moderate or severe in degree, it is easy to treat PPT, by employing beta – blockers for the hyperthyroid phase and levothyroxine for the hypothyroid phase of the disorders (Roti & Emerson, 1992).

Antithyroid drugs are not useful in PPT during hyperthyroid phase because thyrotoxicosis is secondary to hormone release from damaged gland. Observation is important because many patients

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become hypothyroid before recovering normal thyroid function, and patients who recover from PPT should be warned of the increased risk of recurrence with future pregnancies, and of developing permanent hypothyroidism in the future (Othman *etal.*, 1990, Gerstein; 1990 Roti & Emerson., 1992).

1.17 Intervention Prevention

The impact of levothyroxine therapy on the short – and long–term complications of postpartum thyroiditis is largely unknown. Beta blockers during the hyperthyroid phase and levothyroxine therapy in women who are hypothyroid are effective interventions. However, whether or not levothyroxine therapy alters the incidence or severity of the depression associated with postpartum thyroiditis has not been evaluated (Amino *etal.*, 1999).

Studies attempting to prevent the occurrence of PPT through the administration of iodide or levothyroxine in antibody positive women have been unsuccessful (Kampe *etal.*, 1990).

Furthermore, at present there are unknown interventions which can gave administered during the hyperthyroid or hypothyroid phase, would result in a decrease in the high rate of permanent hypothyroidism.

A recent study has demonstrated a decrease in the rate of recurrent abortion in women who were thyroid antibody positive through the administration of intravenous immunoglobulin before conception and throughout the first 8 months of pregnancy (Kiprov *etal.*, 1996). Replication of these results is required before their implementation outside of a research setting.

1.18 Aim of Study

As the reported prevalence of PPT varies from 1 % to 17 %, the diversity in prevalence is due to several factors such as geographic

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differences, differences in duration of follow – up and so on, it is important to indicate the size of the problem in Palestine. To my knowledge, no study on PPT incidence and its impact among Palestinian women had been done.

I was encouraged to at look the problem aiming at:

- Determining the incidence of PPT through pregnant women in Palestine.
- Conducting an appropriate follow – up and management for women with PPT and study the relation between natural lactation with PPT.
- Investigating the size of problems accompanied with PPT.
- Searching for associated risk factors in connection with PPT.
- Determining the impact of heavy metals such as lead (Pb) on thyroid hormones.

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Chapter Two

Materials and Methods

2.1 Study Population and Blood Sampling

We began collection of blood samples for the first interval in (trimester) of gestation in April 2000, and second samples until May 2001, with collaboration of maternal and child health medical centers, and labs. Blood samples were collected and kept in refrigerator, which then arranged and transfer to laboratory to be tested. Briefly 101 pregnant women were screened, blood samples were taken for test at (30-36) weeks of gestation, and at (9-20) weeks postpartum period for the same woman.

Women in this study were contacted individually by telephone, visiting the maternal and child health medical centers and medical labs.

Giving a second blood sample after 2 months or more postpartum, this denote to an agreement of women to do the test and to be one individual of the population of study. Also, a permission from the Ministry of Health was obtained before collection of blood samples is begun.

While blood samples were collected, we began with more than 250 pregnant women gave the first blood sample at gestation period, but at the second sample interval (postpartum)as the conditions in West Bank were strongly bad, we hardly obtain the studied samples (although, there was continuous contact) because :

- women may decline to say "I don't want to share with study.
- Intifadah in West Bank and Gaza decrease the visiting of women to medical centers because there is close up of roads and streets between towns, villages, and cities.

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2.2 Gamma Counter (DPC Gamma-C12)

Gamma counter is an instrument designed for the quantitative analysis of the radioactivity of gamma-emitting nuclides. It is used mainly for clinical in vitro tests –for example, radioimmunoassay (RIA) and immunoradiometric assay (IRMA), but is also generally applicable for all radiochemical measurements involving gamma sources up to medium energy levels.

In this study DPC-Gamma-C12 gamma counter was used in order to measure TSH level for pregnant women studied samples.

2.3 TSH immunoradiometric assay (IRMA) procedure

1- All reagents and samples were allowed to reach room temperature and mixed thoroughly before use.

2- Assay of standard, controls and unknown samples was in duplicate.

3- Two plain (uncoated) tubes were labeled for total counts.

4- Anti-TSH coated tubes were labeled and arranged in duplicate.

5- 0.1ml of the standards, controls or samples was added to the appropriate coated tube.

6- 0.1 ml of the Anti-TSH (I^{125}) reagent was added to each tube.

7- All tubes were shaken gently for 1-2seconds, and then incubated on a shaker set at 180rpm for 2 hours at room temperature (~25C°).

8- Except total count tubes, all tubes were aspirated or decanted by simultaneous inversion with a sponge rack into a radioactive waste receptacle, and blotting the tubes were done to remove any adhering droplets to the rim before returning them to the upright position.

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9- Approximately 3 ml of diluted wash buffer was added to each tube, except total count tubes, decant as described in step 8 and wash for final 3 times were done.

10- All tubes were counted in DPC gamma-C12 for one minute.

11- Results were calculated by using a log-log curve fit.

A-the net counts per minute (net CPM) was calculated by subtracting the mean counts per minute (mean CPM) of the 0mlu/ml TSH standard from the mean CPM of each standards, control, and samples. Calculation of %B/T for each standard, control, and samples was done as follows:

%B/T =Net CPM x 100/Mean Total CPM

B-A curve of the %B/T for each standard (Y-axis) against the TSH concentration (X-axis) on log-log graph paper was done.

C-TSH concentration of the means of duplicate counts for each sample was determined based on standard curve as in B above.

2.4 Radioimmunoassay why?

Because most hormones are present at exceedingly low concentrations in biological materials, they cannot be quantified by standard methods, such as fluorescence measurements or high–performance liquid chromatography (HPLC). Moreover, a hormone is usually surrounded by excessive amounts of chemically related substances, which would interfere with standard analytical techniques.

The principle of radioimmunoassay is quite simple; first determines the radioactivity bound to a small amount of antibody after that antibody is incubated with a large excess of radiolabeled antigen at a known specific activity. In this case the antigen is the hormone TSH being assayed. To generate a standard curve, which relates reduction in bound radioactivity to amount of nonradioactive hormone

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or other antigen, one then incubates the same quantities of antibody and radiolabeled antigen with a known quantity of nonradioactive hormone. The unlabeled hormone competes with labeled hormone for binding sites on the antibody molecules. Thus, the bound radioactivity decreases. This operation is carried out with increasing amounts of nonradioactive hormone (Van Vunakis&Langone, 1980, Yalow, 1978).

2.5 Screening methodology

It is the objective of screening programs to detect women with PPT. Different screening strategies have evolved to detect them. Some had measured TSH, T4, others TSH, T4, and TPO-Ab either in all specimens or on a selective basis.

There are arguments in favor and against using either TSH, T4, or TSH, T4 and TPO-Ab as the preliminary screening.

Thyroid stimulating hormone (TSH) was determined quantitatively by immunoradiometric assay (IRMA) using diagnostic Systems Laboratories,Inc (DSL)-5300.

The cut off point used as criteria for:

- Hypothyroidism when the TSH level is more than 5.1mlu/ml.
- Hyperthyroidism when the TSH level is less than 0.5mlu/ml.

2.6 Assay

Blood samples were taken for TSH test at gestation period in (trimester) and through postpartum period. TSH concentrations were measured by immunoradiometric assay (IRMA) on gamma counter DPC gamma- C-12.

2.7 The Incidence of PPT in West bank

The incidence of PPT was determined by dividing the numbers of suspected affected cases by the total number of the screened subjects.

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2.8 Questionnaire

Simple questionaire was written for some informations about the pregnant women related to thyroid and postpartum thyroiditis study see appendix 1.

2.9 Statistical methods

Data were analyzed using the SPSS (Statistical Package for Social Sciences).Data analysis procedures included both descriptive and inferential statistics.

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Chapter Three

Results

Although the incidence of PPT has been shown to vary among different parts of the world as shown in the table 1.4, it occurs in 5-9% of unselected women during the first year postpartum (Lazarus, 1998; Sakaihara *etal.*, 2000).

Women should be follow–up, including clinical examination, determination of serum T4 and TSH. Early diagnosis and treatment are highly effective, limits the duration of hypo / hyper thyroidism and so the thyroid hormones had been in the normal ranges.

3.1 Data and TSH concentrations Result:

All information in the questionnaire we had were put in table 3.1,which grouped to columns for the age of pregnant women which were divided to 3 age groups (15-20,21-30, and >31 years), during the third trimester of pregnancy (eighth, ninth) prenatal period in month, thyroid gland disease (yes, no) occurrence, pregnant women relatives especially females (yes, no), therapy for thyroid or other diseases (yes, no) postpartum period in month (at least 2 months after birth) breast feeding (yes, no), concentration of lead in μg/dl (grouped to 0, 1-10, 11-20, 21-30, 31-40 &>41) for postpartum period samples, and the TSH concentration in mlu/ml for serum samples of pregnant women before birth and after birth.

Then these data were analyzed on SPSS (Statistical Package for Social Sciences) program for correlations, frequency, and analysis of variance (ANOVA). And TSH test for 101pregnant women is continued for five days.

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Table 3.1: Data and information from questionnaire, and TSH values concentrations result for prenatal and postpartum periods to 101pregnant women.

#	Age	Pregnant month	Thyroiditis	Relative	Breast feeding	Remedy	Month after birth	Lead (µg)\dl	TSH(mlu/ml)before	TSH(mlu/ml)after
1	21-30	Eighth	No	No	Yes	No	3	.	.8	.7
2	21-30	Ninth	No	Yes	Yes	No	5		.3	.1
3	21-30	Ninth	No	No	yes	No	2	11-20	1.3	1.6
4	21-30	Ninth	No	No	Yes	No	5	11-20	.8	1.1
5	≥31	Eighth	No	No	Yes	No	4.5	11-20	2	1.1
6	21-30	Ninth	No	No	Yes	No	6	11-20	.8	.7
7	21-30	Eighth	No	No	Yes	No	2	11-20	3.4	1.6
8	21-30	Ninth	No	No	Yes	No	3	11-20	2.3	1.1
9	21-30	Ninth	No	No	Yes	No	2	11-20	1.7	.3
10	21-30	Ninth	No	No	Yes	No	2		2.8	.2
11	21-30	Ninth	No	No	Yes	No	2		1	2.2
12	21-30	Ninth	No	No	Yes	No	5		.9	.3
13	21-30	Eighth	No	No	Yes	No	3		.4	.7
14	21-30	Eighth	No	No	Yes	No	3		1	0.00
15	21-30	Ninth	No	Yes	Yes	No	3		3.4	.8
16	21-30	Ninth	No	No	Yes	No	2		2.6	.9
17	21-30	Ninth	No	No	No	No	5		.7	.8
18	21-30	Eighth	No	No	Yes	No	2		.6	.1
19	≥ 31	Eighth	No	No	Yes	No	2		1.7	1.1
20	15-20	ninth	No	No	Yes	No	2	.	1.6	.9
21	21-30	Eighth	No	No	Yes	No	2	0	.8	1.4
22	21-30	Eighth	No	No	Yes	No	2	11-20	1.1	.8
23	15-20	Eighth	No	No	Yes	No	2	.	1.7	2
24	≥ 31	Eighth	No	No	Yes	No	2	31-40	.4	.4
25	≥ 31	Eighth	No	No	Yes	No	2	11-20	1.7	1.5
26	21-30	Eighth	No	No	Yes	No	2	11-20	1.6	1.1
27	≥ 31	Eighth	No	No	Yes	.	2	.	1.1	.4
28	21-30	Eighth	No	No	Yes		2	.	.9	.6
29	≥ 31	Eighth	No	No	Yes	.	2	31-40	1.2	.5
30	21-30	Eighth	No	No	Yes		2	11-20	1.8	.5
31	≥ 31	Ninth	No	No	Yes	Yes	2	11-20	.2	.8
32	21-30	Ninth	No	No	Yes	No	2	11-20	1.6	2.9
33	21-30	Eighth	No	No	Yes	No	2	.	.5	1.3
34	21-30	Eighth	No	No	Yes	No	2	11-20	2.0	2.8
35	≥ 31	Eighth	No	No	Yes	No	2	11-20	.1	.7
36	21-30	Eighth	No	No	Yes	No	2	6	1.6	1.2
37	≥ 31	Ninth	No	No	Yes	No	2	11-20	1.7	1.2
38	≥ 31	Ninth	No	No	Yes	No	2	11-20	1.5	.7
39	21-30	Ninth	No	No	Yes	No	2	6	1.8	.2
40	21-30	Ninth	No	No	Yes	No	2	0	.9	.1
41	21-30	Ninth	No	No	Yes	No	2	11-20	1.5	3.4
42	21-30	Ninth	No	No	Yes	No	2	11-20	1.1	2.1
43	≥ 31	Ninth	No	No	Yes	No	2	11-20	.4	.6
44	21-30	Ninth	No	No	Yes	No	2	11-20	1.2	1.8
45	21-30	Ninth	No	No	Yes	No	2	.	1.7	1.5
46	15-20	Ninth	No	Yes	Yes	Yes	2	11-20	5.2	4
47	21-30	Ninth	No	No	Yes	No	2	11-20	3.6	1.6
48	21-30	Ninth	No	No	Yes	No	3	11-20	1.7	.7
49	21-30	Ninth	No	No	Yes	No	2	11-20	.7	.2

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50	15-20	Ninth	No	No	Yes	No	2	.	2.7	1.3
51	≥ 31	Ninth	Yes	No	Yes	No	2	11-20	1.2	.6
52	21-30	Ninth	No	No	Yes	Yes	2	11-20	1.4	1.78
53	≥ 31	Ninth	No	No	Yes	No	2	11-20	.3	1.5
54	15-20	Ninth	No	No	Yes	No	2	11-20	.1	1
55	21-30	Ninth	No	No	Yes	No	2	11-20	3.3	3.6
56	21-30	Ninth	No	No	Yes	No	2	11-20	1	1
57	21-30	ninth	No	No	Yes	No	2	21-30	1.2	2.1
58	21-30	Ninth	yes	No	Yes	No	2	11-20	.4	.7
59	21-30	Ninth	No	No	Yes	No	3	11-20	1.1	1.5
60	21-30	Ninth	.	.	Yes	No	2	11-20	1	2.3
61	21-30	Ninth	No	No	Yes	Yes	2	11-20	.7	2.7
62	21-30	Eighth	No	No	Yes	No	2	11-20	3.8	3.7
63	21-30	Ninth	No	No	Yes	No	2	.	2	1.8
64	≥ 31	Ninth	No	No	Yes	No	2	11-20	1.5	1.2
65	21-30	Ninth	No	No	Yes	No	2	0	2.1	2.7
66	21-30	Ninth	No	No	Yes	Yes	2	11-20	.4	1.2
67	≥ 31	Eighth	No	No	Yes	No	2		.3	.6
68	21-30	Eighth	No	No	Yes	No	2	.	4.1	1.5
69	≥ 31	Eighth	No	No	Yes	No	2	.	.7	1.2
70	≥ 31	Eighth	No	No	Yes	.	2	.	1.2	1
71	21-30	Eighth	No	No	Yes	.	2	.	.4	1.4
72	21-30	Ninth	No	No	Yes	Yes	2	.	.9	3.6
73	≥ 31	Eighth	No	No	Yes	.	2	.	3.5	5
74	21-30	Eighth	No	No	Yes	No	2	21-30	.1	.1
75	21-30	Ninth	No	No	Yes	No	2	.	.4	.8
76	15-20	ninth	No	No	Yes	No	2	.	5.1	1.7
77	21-30	Eighth	No	No	Yes	No	2	.	.9	1.3
78	≥ 31	Ninth	No	No	Yes	No	2	.	1	0.0
79	≥ 31	Ninth	No	No	Yes	.	2	.	.3	.3
80	21-30	Eighth	No	No	Yes	No	2	.	1.8	1.5
81	21-30	Eighth	No	No	Yes	No	2	.	1.2	0.0
82	15-20	Eighth	No	No	Yes	.	2	.	2.5	4.1
83	≥ 31	Eighth	No	Yes	Yes	No	2	11-20	.8	1.8
84	15-20	Ninth	No	No	Yes	No	2	.	1	2.3
85	21-30	Ninth	No	No	Yes	.	2	31-40	1.5	2.7
86	≥ 31	Ninth	No	No	Yes	.	2	21-30	.3	3.2
87	21-30	Eighth	No	No	Yes	No	2	.	2.4	2.2
88	≥ 31	Eighth	No	No	Yes	.	2	41-above	1.1	.2
89	21-30	Eighth	No	No	Yes	.	2	.	2.4	2.3
90	21-30	Eighth	No	No	Yes	No	2	41-above	.6	1.2
91	≥ 31	Eighth	No	No	Yes	No	2	41-above	.6	3.2
92	21-30	Ninth	No	No	Yes	No	2	11-20	1.2	1.7
93	15-20	Eighth	No	No	Yes	No	2	21-30	1.2	1
94	21-30	Ninth	No	No	Yes	.	2	31-40	.2	2.7
95	21-30	eighth	No	No	Yes	.	2	.	1.8	1.4
96	21-30	Eighth	No	No	Yes	No	2	6	1	1.7
97	21-30	Eighth	No	No	Yes	.	2	21-30	.6	1.5
98	15-20	Ninth	No	No	Yes	.	2	.	1.2	1.2
99	21-30	Eighth	No	No	Yes	No	4	.	.7	.4
100	21-30	Eighth	No	No	Yes	No	3	.	.7	.7
101	21-30	eighth	No	No	Yes	No	2	.	1.1	0.0

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3.1.1 Incidence of PPT in West Bank

Table 3.2 shows that 50(49.5%) of screened cases had decreased (according to prenatal reference TSH level) in TSH concentration in postpartum period, 45 (44.6%) of screened cases had increased in TSH, 6(5.9%) of screened cases had no changed in TSH level, and 4(4%) of 101 cases screened; had undetectable TSH concentration.

It is worth noting that the majority of the previously mentioned subjects, 94.1%of cases had changed in TSH concentration in postpartum period (decreased or increased), and 4cases from 101 cases screened that were initially diagnosed as having PPT.

Based on the number of pregnant women screened during the period of the study, the overall incidence rate of suspected PPT among the tested population in West Bank was at least 4%, PPT cases were with diminished TSH concentration (hyperthyroidism phase).

Table 3.2: Percentage of cases decreased and increased in TSH concentration through postpartum period

	Decrease	increase	No change	undetectable
#of cases (percentage %)	50(49.5%)	45(44.6%)	6(5.9%)	4(4%)

3.2 TSH concentrations:

Table 3.3 shows that the frequency and percentage of pregnant women screened for TSH concentrations, in the period before birth (prenatal), 1(1%) of cases were hypothyroidism, 17(16.8%) of cases were hyperthyroidism, and 83(82.2%) of cases had normal thyroid function.

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Table 3.3: Percentage and Frequency of hypothyroidism, hyperthyroidism, and normal thyroid function for pregnant women in prenatal period (before birth).

Prenatal period	#of cases(percentage)
Hypothyroidism	1(1%)
Hyperthyroidism	17(16.8%)
Normal	83(82.2%)

Table 3.4 shows that no any case was hypothyroidism, and 18(17.8%) of cases were hyperthyroidism, and 83(82.2%) were normal for TSH concentration through postpartum period.

Table 3.4: Frequency and percentage of hypothyroidism, hyperthyroidism, and normal thyroid function for women screened for TSH in postpartum period.

Postpartum period	# of cases (percentage%)
Hypothyroidism	0.0(0%)
Hyperthyroidism	18(17.8%)
Normal	83(82.2%)

3.3 Biostatistical Analysis:

Data presented in table 3.5, A, B, shows that the mean of TSH for pregnant women (prenatal period) was 1.3901mlu/ml, and the mean of TSH concentrations for postpartum period was 1.3810mlu/ml, and correlation between the mean of TSH concentration before and after birth

Table 3.5: (A) Mean of TSH

	mean
TSH (mlu/ml) before delivery	1.3901
TSH (mlu/ml) after delivery	1.3810

3.5B :

	t	df	Sig.(2-tailed)
TSH (mlu/ml) before - TSH (mlu/ml) after	0.081	100	0.936

Depending on T- test dependant samples, and as shown in tables(3.5 A,B),t value is 0.081,level of significance is 0.936,degree of

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freedom is 100.This data denote that there is no significance difference between TSH concentrations through prenatal period and postpartum period.

3.4 Correlations Tables between TSH and heavy metals (lead) concentrations.

Table 3.6 A shows the mean concentrations of lead (μg/dl) for 58 samples of pregnant women whom screened for postpartum thyroiditis. And the correlations between mean of TSH for prenatal period and mean concentrations of lead (μg).And table 3.6 B shows the correlation between the mean of TSH concentration before birth and the mean of lead concentration (μg/dl).As mentioned, the mean of TSH concentration before birth is 1.3901mlu/ml, and the mean of lead concentration in serum is 2.5690μg/dl for 58 women in postpartum period. It is noted that, Pearson correlation factor is - 0.152, and significant level is 0.253.This values mean that there was no statistically significant correlation between the mean of TSH and the mean of lead concentration.

Table 3.6 (A): The mean of lead concentration and the mean of TSH values before birth.

	mean	N
Lead (μg/dl)	2.5690	58
TSH (mlu/ml) before delivery	1.3901	101

3.6 (B) :Correlations between lead concentration mean and mean of TSH values before birth .

		Lead μg/dl	TSH (mlu/ml) before
Lead μg/dl	pearson correlation	100	-0.152
	Sig. (2-tailed)	.	0.253
	N	58	58
TSH (mlu/ml) before	pearson correlation	-0.152	1.00
	Sig. (2-tailed)	0.253	.
	N	58	101

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Table 3.6 (C): One way analysis of variance (ANOVA) for TSH values before and after birth and lead concentration .

	F	SIG
TSH (mlu/ml) before	5.135	0.008
TSH (mlu/ml) after	1.904	0.154
µg/dl lead	0.144	0.866

Data presented in table 3.6 (C) represents the analysis of variance ANOVA test, the results show that F value is 5.135 with respect to TSH concentrations before birth and significance level is 0.008, this means that there was statistically significant variance between the three groups that the values are divided to it. Also, the test for TSH values after birth shows that F value is 1.904 and the significance level is0.154, this mean that there was no statistically significant variance between the three groups that the values are tabled. Respectively, to the values of lead, F value was 0.144 and significance level 0.866, also no statistically significant variance between the three groups values.

3.5 Frequency Tables

The data we had for screening pregnant women in West Bank for postpartum was tabled in table 3.1, and this, was tabled in frequency tables as shown in tables 3.7, 3.8, 3.9, 3.10, 3.11, 3.12, for age, month before birth (prenatal) period, postpartum period, breast feeding, TSH concentrations before birth, and TSH concentrations after birth respectively.

Table 3.7 shows the frequencies for age of pregnant women that screened through this study, 10 women were in the age 15-20 year,67 women were in the age 21-30 year , and 24women were in the age ≥ 31 .

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Table 3.7: Frequency of pregnant women with respect to the age in years.

Age	frequency	Percentage %
15-20	10	9.9
21-30	67	66.3
≥ 31	24	23.8
Total	101	100.0

Table 3.8 shows the percentage and frequency of pregnant women for the prenatal period, before birth in trimester, 46 women were in the eighth month, and 55 women were in the ninth month.

Table 3.8: Frequency of subjects with respect to time of test in month prenatal.

Month in prenatal	frequency	Percentage %
Eighth	46	45.5
Ninth	55	54.5
Total	101	100.0

Table 3.9 shows the frequency of pregnant women according to the postpartum period, serum samples were collected at least 2 months after birth, when women in postpartum the questionnaire is written and closed. In table, 86 women were in 2months after birth, 8 women were in 3 months interval, one only in 4 month after birth interval, also one for 4.5, 6 months interval, and 4 women in 5 months after birth interval.

Table 3.9: Frequency of subjects with respect to the month in postpartum period.

Month in postpartum	frequency	Percentage %
2	86	84.2
3	8	8.9
4	1	1.0
4.5	1	1.0
5	4	4.0
6	1	1.0
Total	101	100.0

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Table 3.10 show that 99 % of women screened for postpartum study in 2 –6 months after birth were still feed their baby by breast feeding.

Table 3.10: Percentage and frequency for breast feeding.

Breast feeding	Frequency	Percentage %
Yes	100	99
No	1	1.0
Total	101	100

Table 3.11 show the frequency of pregnant women that screened for TSH concentrations in the eighth and ninth month before birth. The TSH concentrations was in mlu/ml and the intervals was divided as 0.1, 0.2, 0.3,0.4,....., 5.2. The frequency for each interval as shown in the table. However, 16.8% cumulative percentage of pregnant women were had TSH concentration less than 0.5mlu/ml, and only one case had TSH concentration more than 5.1mlu/ml.

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Table 3.11: Frequency of samples for TSH concentrations (mlu/ml) in prenatal period (before birth).

TSH (mlu/ml)	frequency	percentage %
.1	3	3.0
.2	2	2.0
.3	5	5.0
.4	7	6.9
.5	1	1.0
.6	4	4.0
.7	6	5.9
.8	5	5.0
.9	5	5.0
1	7	6.9
1.1	6	5.9
1.2	9	8.9
1.3	1	1.0
1.4	1	1.0
1.5	4	4.0
1.6	4	4.0
1.7	7	6.9
1.8	4	4.0
2	3	3.0
2.1	1	1.0
2.3	1	1.0
2.4	2	2.0
2.5	1	1.0
2.6	1	1.0
2.7	1	1.0
2.8	1	1.0
3.3	1	1.0
3.4	2	2.0
3.5	1	1.0
3.6	1	1.0
3.8	1	1.0
4.1	1	1.0
5.1	1	1.0
5.2	1	1.0
Total	101	100.0

Table 3.12 shows the frequency and percentage of women according to the TSH concentration after birth, 4 cases were undetectable TSH concentrations, with cumulative percentage 4.0 %, and 17.8% (cumulative) of cases had TSH concentration less than 0.5 mlu/ml.

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Table3.12: Percentage and frequency of women for TSH concentration (mlu/ml) in postpartum period (after birth).

TSH (mlu/ml)	frequency	percentage %
0.00	4	4.0
0.10	4	4.0
0.20	4	4.0
0.30	3	3.0
0.40	3	3.0
0.50	2	2.0
0.60	4	4.0
0.70	8	7.9
0.80	5	5.0
0.90	2	2.0
1.00	4	4.0
1.10	5	5.0
1.20	7	6.9
1.30	3	3.0
1.40	3	3.0
1.50	7	6.9
1.60	3	3.0
1.70	3	3.0
1.78	1	1.0
1.80	3	3.0
2.00	1	1.0
2.10	2	2.0
2.20	2	2.0
2.30	3	3.0
2.70	4	4.0
2.80	1	1.0
2.90	1	1.0
3.20	2	2.0
3.40	1	1.0
3.60	2	2.0
3.70	1	1.0
4.00	1	1.0
4.10	1	1.0
5.00	1	1.0
Total	101	100.0

Table 3.13 shows descriptive statistics clearing the variances tabled in table 3.1, minimum and maximum values for each variable, also the mean.

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Table 3.13 : Descriptive

	N	Minimum	Maximum	Mean
Age	101	1.0	3.00	2.1386
Pregnance month	101	1.0	2.00	1.5446
Suffer thyroidities	100	1.0	2.00	1.9800
Exist	100	1.0	2.00	1.9600
Remedy	86	1.00	2.00	1.9302
After birth	101	2.00	6.00	2.2921
Breast feeding	101	1.00	2.00	1.0099
µg/dl	58	1.00	6.00	2.5690
TSH mlu/ml before	101	0.10	5.20	1.3901
TSH mlu/ml after	101	0.00	5.00	1.3810

Graph 3.1 show a diagram for TSH concentration values (mlu/ml) for prenatal and postpartum periods, minimum and maximum values for each are cleared.

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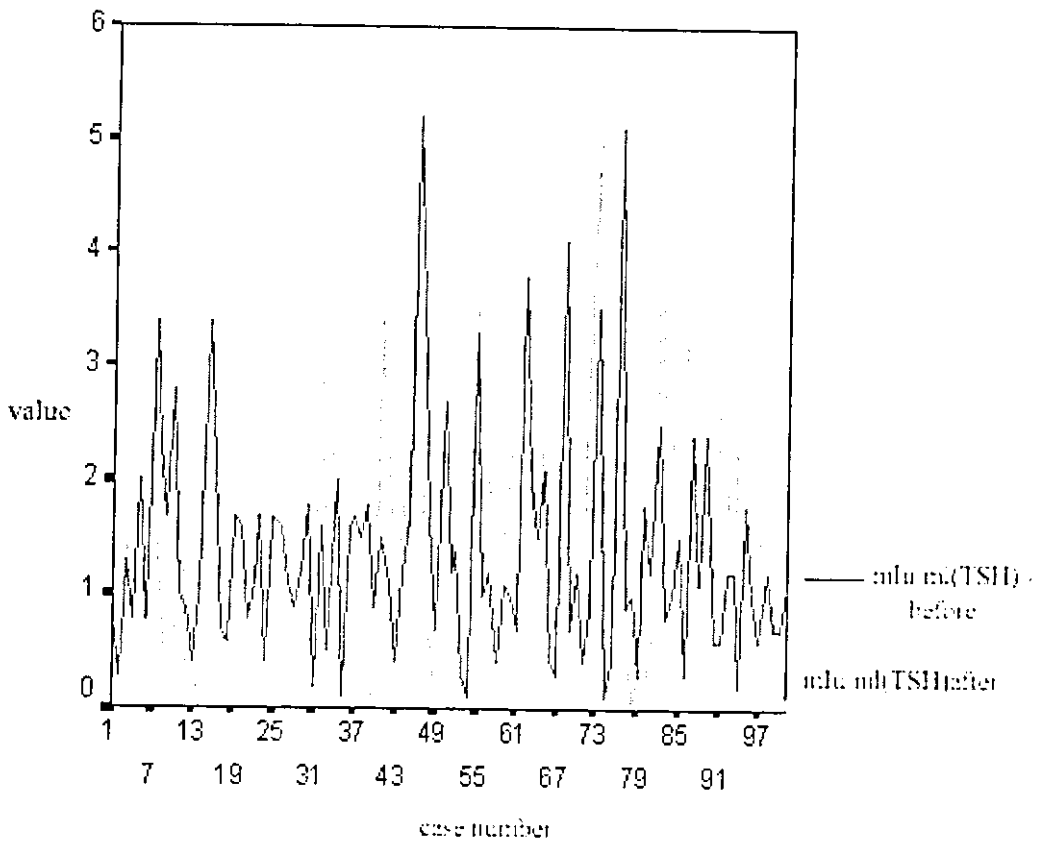
Figure 3.1: Diagram for TSH concentrations before and after birth.



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Chapter Four

Discussion

Pregnancy has an important modifying influence on disease activity in women with autoimmune disease. Although a consistent beneficial effect is found in connective tissue disorders, disease often progresses rapidly during pregnancy and is sometimes exacerbated postpartum. Published studies however report a bewildering variety of frequency for the effect of pregnancy on the maternal course of disease (Imai *etal.*, 1996).

The prevalence of PPT in the general population ranges from 1.1-16.7% (Amino et al., 1999). In our study excluding women who had a history of thyroid disease or thyroid dysfunction during pregnancy, the prevalence of PPT was found to be 4.0%

4.1 Screening Program

As there is no any screening program for PPT in Palestine, this current study represents a base line data on the status of PPT among Palestinian pregnant women in west bank. Only 101pregnant women in west bank were screened during the study period from May 2000 to May 2001.

A possible explanation for this status could be due to the followings:

- prevailing political situation.
- poor awareness on the importance of screening program.
- Asymptomatic of PPT, so there is no attention to the disease.
- Any screening program, need too big budget which is not abundant.
- Inadequate primary health care in postpartum period from physicians and women in west bank.
- Nature of screening program, there is more than one drawing blood samples through long period (2-6) months and this would definitely

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reflected on the possibility of giving more than one sample, which is need in screening and follow up the cases, for example, in this study there was more than 250 first blood sample, but when we need a second blood sample, only 101 subjects showed interest.

One thus can conclude that, with increasing public awareness on PPT and emphasize on the importance of early diagnosis of diseases, is most likely to improve outcome of treatment.

4.2 Biochemical and clinical findings of the study cases

The presence of thyroid stimulating hormone TSH (thyrotropin) is necessary for the progression of several thyroid diseases. The first and most sensitive indicator of thyroid deficiency is an increase in the serum TSH concentration which occurs before any decline in serum thyroid hormone concentrations (Braverman *etal.*, 1991).

With blood lead concentrations of greater than 70μg/dl and clinical lead poisoning syndromes–presented with diminished T4 and estimated free T4, inappropriately low TSH levels (Schumacher *etal.*, 1998), the absence of an association between thyroid dysfunction and lead exposure resulting in blood levels of less than 60μg/dl appears to be a consistent finding in this and other studies.

Wide variation exists in the clinical features of autoimmune thyroiditis (Livolsi & Logerfo, 1981). Many patients have no clinical signs or symptoms, and the diagnosis is made only on the basis of tests of thyroid function or of thyroid antibodies done for screening purposes, or by unexpected operative or biopsy finding of lymphocytic infiltration of the thyroid. In other patients, an enlarged thyroid is only clinical manifestation of the disorder (Livolsi & Logerfo, 1981).

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Pregnant women screening and confirmatory thyroid stimulating hormone TSH results revealed simple abnormalities in nearly18% of cases see table 3.1.

The mean value of TSH was clearly 1.3901mlu/ml for pregnant women in prenatal period and 1.3810mlu/ml for women in postpartum period. These values emphasized by the serum TSH concentration tend to increase slightly during gestation, see table 1.1, and this also symmetry with information in table 3.3 and table 3.4. Exactly, 82.2% of cases had a marked normal TSH concentration in prenatal period, 16.8% of cases had a marked TSH concentration less than 0.5mlu/ml and 1.0% of cases had TSH concentration more than 5.1mlu/ml see table 3.3. Coresponding to postpartum period interval, 82.2 % of cases had normal TSH concentration, but 17.8% of cases had marked TSH concentrations less than 0.5 mlu/ml see table 3.4.

Only 4(4%) samples had very low concentration or undetectable level of TSH, see cases numbers(14,78,81,101), these values could be attributed, in one part, to the occurrence of the disease and on the other hand, to the hyperthyroidism phase. And more than 94% of cases had a changed in TSH level in postpartum period (decreased or increased), this need more follow up. However, we had 18(17.8%) cases had to classified in hyperthyroidism phase (included cases with undetectable TSH level). Also, we had 4(4%) cases were hyperthyroidism in prenatal interval and continued hyperthyroidism in postpartum period, see cases numbers (2, 24, 74, 79) in table 3.1. And 13(12.9%) cases were hyperthyroidism in prenatal interval had classified to normal phase in postpartum period, see cases numbers (13, 31, 35, 53, 54, 58, 66, 67, 71, 75, 81, 86, 94) in table 3.1.

All studied cases 4(4%) were with decrease serum TSH and were undetectable TSH concentration and accordingly they were suspected to have PPT.

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Cases with normal level of TSH (0.5-5.1)mlu/ml may had postpartum thyroiditis as the blood collection period had a wide range 2–6 months, and in some patients the thyrotoxic or hypothyroid phase either does not occur, or is not recognized (Luboshitzky *etal.*, 1998). So, hypo or hyper thyroidism may occur later on. Unfortunately follow up to these cases is not possible because of limitations on time and budget. These cases show a hyperthyroidism which is transient phase, followed perhaps by hypothyroidism (Lazarus, 1998). This point deserves further investigations.

It is well known that all women with PPT appear normal and with no clinical signs or symptoms. It is possible that women don't give attention to the PPT symptoms because it is difficult to distinguish between postpartum period symptoms and PPT symptoms. Symptoms during hyper/hypo thyroiditis phase of disease are often mild in degree and brief in duration (Amino *etal.*, 1999).This emphasize the importance of biochemical screening in detection and diagnosis of PPT.

However, in this study therapy was not considered in all cases, as it is not useful to give antithyroid drugs because thyrotoxicosis is not the result of increased thyroid hormone synthesis, but of discharge of thyroid hormone from the thyroid gland due to the inflammatory process. The effect of propylthiouracil or iopanoic acid to block peripheral T4 to T3 conversion may be of some clinical benefit. If more serious thyrotoxicosis is present, administration of anti-inflammatory drugs may be of benefit.

4.3 Transient Hyperthyroidism

In addition to the previously found PPT cases , our findings on transient hyperthyroidism rate seems fairly high as shown in table 3.4 .It is important to note that screening programs for PPT indicate that hyperthyroidism phase occurring first (transient) then hypothyroidism phase (Lazarus, 1998).

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Iodine deficiency seems to have no effect on hyperthyroidism phase in PPT cases. So, patients should be followed up since their thyroid status usually is unstable (Fung *etal.*, 1988; &Lazarus, 1996).

Recommendations and Concluding Remarks

The purpose of our study is to alleviate symptoms from hypothyroidism and transient hyperthyroidism and to identify women who are at risk for subsequent permanent hypothyroidism, as well as PPT in future pregnancies.

All postpartum women, whether or not screening is done, should be encouraged by their physicians to seek medical attention if they have troublesome symptoms and not automatically attribute a lack of well-being to the postpartum state.

Comprehensive studies on pregnant women that associated with postpartum thyroiditis are still needed and further follow up studies are needed to determine intellectual quotient of PPT cases.

Pregnant women should have routine monitoring of thyroid gland hormones and antibodies (TPO), during pregnancy and postpartum period for the PPT affected cases, and a long follow up of affected cases to establish a firm and final diagnosis of transient/permanent hypo/hyperthyroidism phase. A through out biochemical tests, clinical signs and symptoms of PPT, should be used to rapidly establish the diagnosis.

An effective mechanism should be established at all facilities levels to increase awareness of physicians, people towards screening tests and their advantages to PPT cases.

An effective mechanism should be established at all facilities levels to increase the care with medical researches through increasing primary health care centers and increase awareness of people towards screening tests and their advantages .

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الفحص خلال فترة الدراسة ، وهي من مايو ٢٠٠٠ ، الى مايو ٢٠٠١ لها مستويات من هورمون TSH اقل من (0.5mlu/ml)، بما يشير الى اننا بحاجة الى متابعة لفترة اطول لهؤلاء النسوة ، وبحاجة إلى دراسة أوسع مما يتطلب ميزانيات أكبر لمتابعة إجراء مثل هذا المسح على التهابات الغدة الدرقية بعد الولادة.

وجدير بالذكر ، انه تم هذا المسح بعمل فحص هرمون (TSH) للنساء الحوامل ، حيث تم تحديد مستويات الهورمون قبل الولادة ، وفحص آخر لتحديد مستوياته بعد الولادة ،عن طريق استخدام طريقة(IRMA) وفيما يتعلق بمسببات هذه الحالة المرضية فلا زالت غير محددة وغير واضحة ، قد تكون نتيجة أسباب عديدة ومتداخلة ، ذلك ان هذه الحالة المرضية تعزى إلى المناعة الذاتية ووجود أجسام مضادة ضد (TPO).

وبعد هذه الدراسة نستنتج أننا بحاجة إلى عمل برنامج خاص لمثل هذه الحالة المرضية لجميع النساء الحوامل ، حيث يجرى لهن فحص (TSH) و (T4) قبل وبعد الولادة ، ويحتفظ بالنتائج وتدون لفترة زمنية طويلة للحصول على تشخيص دقيق وبالتالي معالجة فعالة . ولتحقيق هذا الهدف لا بد من التعاون بين جميع الهيئات المعنية والمؤسسات الصحية لمراكز الأمومة والمرأة الحامل أثناء الحمل وبعد الولادة وتوفير الامكانيات المادية.

على الرغم من ايجابيات برنامج المسح المذ كور للنساء الحوامل الا انه مكلف كثيرا ، ولاسباب تتعلق بالمخصصات المالية للبحث لا نستطيع استكمال بقية التحاليل المطلوبة من اجل تحديد مرض الغدة الدرقية بالضبط.

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التهابات الغدة الدرقية

عند النساء في الضفة الغربية

إعداد:

طلال فايز فريحات.

إشراف

الدكتورمحمد جواد مسمار.

الدكتورة سمر غزال.

الدكتور يحيى فيضي.

الملخص :-

تهدف هذه الدراسة لعمل وتأسيس قاعدة بيانية صحية حول التهابات الغدة الدرقية بعد الولادة عند النساء الحوامل، حيث لا يوجد أي دراسة سابقة حسب علمي حول هذا الموضوع في الضفة الغربية لغاية الانتهاء من هذه الدراسة . وتحقق هذه الدراسة صورة حول مدى انتشار هذا المرض في المجتمع الفلسطيني .

بالرغم من عدم وجود أي اهتمام طبي وتشخيص لهذه الحالة المرضية ، بل هناك جهل عند الناس وعدم معرفة ومتابعة عند الأطباء . بينت نتائج هذه الدراسة أن التهابات الغدة الدرقية بعد الولادة عند النساء الحوامل في الضفة الغربية موجودة ، حيث ظهر (٤) حالات من النساء الحوامل اللواتي تمت الدراسة عليها من مجموع (١٠١) حالة، وتعتبر هذه النسبة قريبة إلى ما هو موجود في العالم ، وتبين أيضا أن ١٧،٨ % من الحالات التي شملها

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Appendix 1

Questionnaire Form

١. الاسم:

٢. تاريخ الميلاد:

٣. العنوان:

٤. رقم التلفون

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٥. حامل بالشهر: أ. الثامن ب. التاسع

٦. هل عانيت مسبقا من اضطراب الغدة الدرقية أو أخذت علاجا لها ؟

أ. نعم ب. لا

٧. المرأة الحامل: هل يوجد هذا المرض عند الأقارب ؟

أ. نعم ب. لا

شهرين تقريبا بعد الولادة:

٨. هل تقومين بالإرضاع الطبيعي لطفلك ؟ أ. نعم ب.لا

٩. ما هو تاريخ ميلاد الطفل/ة ؟

١٠. هل عانيت من أي مرض أو تناولت أي علاج بعد الولادة ؟

أ. نعم ب. لا

١١ . ملاحظات أخرى ترغبين ذكرها عن صحتك ونشاطك بصورة عامة

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